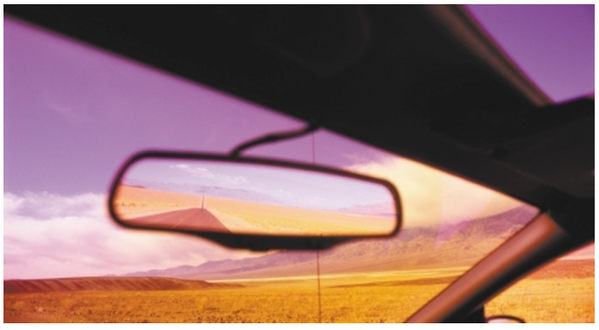

DEVELOPMENT

A rear view of FGF signalling

Much attention has been focused on identifying the signals that specify the anterior nervous system in vertebrates, but surprisingly little is known about the factors that regulate the development of the spinal cord. The favoured model states that early signals specify anterior neural structures, then the more posterior structures develop in response to a transforming signal from the organizer region. Initially, fibroblast growth factor (FGF) signalling looked like a good candidate for the posteriorizing signal, because FGF was shown to activate posterior markers in *Xenopus* neural plate explants. However, other observations were difficult to reconcile with this idea; for example, blocking of FGF signalling in *Xenopus* had little effect on anteroposterior patterning. Now, in a paper published in *Nature Cell Biology*, Mathis *et al.* propose a different but equally important function for FGF signalling in spinal cord development.

The authors showed that in the chick, spinal cord progenitor cells reside in a region of the epiblast adjacent to the organizer, or Hensen's node. During development, the progeny of these cells normally become dispersed along the entire length of the spinal cord as the node progresses caudally. However, if FGF signalling is blocked in a subset of the progenitor cells using a dominant-negative FGF receptor (dnFGFr), the cells expressing this receptor fail to extend to the caudal end of the neural tube, perhaps indicating that they exit the node prematurely. This seems to be a cell-autonomous effect, because cells in the same embryo that express only the wild-type receptor still disperse normally to the tip of the tail bud. Mathis *et al.* suggest that FGF signalling maintains a stem zone of spinal-cord progenitors in the region surrounding Hensen's node. According to their model, the cells divide symmetrically, and half of the cells produced in each round of division are expelled into the neural plate. This seems to be a stochastic event, with the more rostrally positioned cells exiting the node first.

This study serves as a reminder of the importance of the precise coordination of cell movement and growth during development. Although the putative 'posteriorizing signal' still remains elusive, we have certainly gained valuable new insights into the role of FGF signalling in spinal cord development.

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SYNAPTOGENESIS

The chicken, the egg and the NMJ

A long-standing question in the study of the neuromuscular junction (NMJ) concerns the role of the afferent nerve in the formation of this synapse. The identification of agrin as a nerve-derived protein that clusters acetylcholine receptors (AChRs) in the muscle indicated that arrival of the afferent nerve is crucial for synaptogenesis to start. Subsequently, other molecules that act downstream of agrin have been identified so that we now have a relatively clear idea of how the postsynaptic specialization at the NMJ is assembled. But a basic question remains unanswered: does postsynaptic differentiation start before the nerve arrives? In other words, do AChRs cluster in the absence of nerve and nerve-derived agrin? Using genetic methods, Lin *et al*. have recently provided compelling evidence that the answer is affirmative.

Early studies had shown that nerve terminals are always in apposition to AChR clusters. However, Lin *et al*. revisited this conclusion *in vivo* and found that a significant fraction of clusters was actually 'aneural'; presynaptic terminals did not appose them. How did these clusters arise? The authors used several mutant mice to address this question and found that AChR clusters were present in agrin-deficient mice, as well as in HB9 mutant mice in which the phrenic nerve fails to develop. In contrast, clusters were completely absent in mice that lack the molecule known as MuSK, a protein kinase that acts downstream of agrin. These findings indicate that the initial steps of postsynaptic differentiation do not require agrin or the afferent nerve, but are dependent on MuSK activation.

Although AChR clusters can form in the absence of agrin and the afferent nerve, the two conditions are not strictly equivalent. Lin *et al*. found that AChR clusters became smaller with time in the agrin-deficient mice, whereas they increased in size in HB9 mutants. The authors suggested that the nerve not only produces agrin to maintain AChR clusters, but it is also the source of an unidentified signal that disperses receptors that have not been stabilized by agrin.

So, it looks as though there are three steps in the formation of the NMJ. First, aneural clusters are formed in a nerve/agrin-independent, MuSK-dependent early phase. Later on, agrin promotes stabilization of these postsynaptic specializations and the formation of new clusters, while a nerve-derived signal disperses unstable AChR clusters. But what is the role of aneural AChR clusters? Do they attract the incoming axon during synaptogenesis? If this were the case, it would put a new twist on an old dilemma that we thought had been solved for the NMJ: which came first, the chicken or the egg?

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